The point prevalence of an abnormal ankle-brachial index in antiphospholipid antibody negative patients with livedo reticularis: a controlled study

Livedo reticularis (livedo) is characterised by reticular cyanotic cutaneous discolouration surrounding a pale central area. Physiological livedo, also known as cutis marmorata, is common in young women on exposure to cold. Pathological livedo is characterised by a fixed broken pattern, which is occasionally associated with ulceration. Livedo is frequently seen in antiphospholipid (Hughes) syndrome (APS), and appears to be associated with a worse prognosis.[1] A number of patients have recently been described who have many features of APS including thrombosis, livedo and pregnancy morbidity in the absence of antiphospholipid antibodies (aPL).[2] Our aim was to assess the prevalence and clinical associations of an abnormal ankle brachial pressure index (ABPI) in patients with clinical features of APS but who are persistently aPL negative.

We assessed 24 patients referred to our clinic with fixed and extensive livedo spread over at least two of the three sites (ie, upper extremities, lower extremities and trunk), who had recurrent pregnancy morbidity and/or thrombosis who were persistently negative for aPL. A control group of 30 healthy women (aPL negative) of similar age without any livedo were also evaluated. The ABPI was measured according to a consensus statement on methodology.[3]

The median ages of the patients were 42.5 (35–57) and 39 (28–50) years in the control group. A total of 14 had a history of pregnancy morbidity and 16 had previous thrombosis: 11 arterial and 5 venous, 1 had both: all were aPL negative. There was no evidence of other autoimmune diseases. An abnormal ABPI (<1.0) was found in 4/24 (16.2%) patients with livedo compared to none of the healthy subjects (0/30)($p<0.025$). No correlation between abnormal ABPI and traditional cardiovascular risk factors was observed (table 1).

Ehrmann described livedo racemosa with irregular, ill-circumscribed and broken segments, which is considered as pathological. The livedo seen in APS patients can be both, (livedo reticularis and livedo racemosa).[4] Our emphasis is that it is not the type but the extent of livedo that is pathological. Livedo may present in isolation, often associated with stroke, thrombosis, hypertension and cardiac valve abnormalities.[2 5 6]

The pathophysiology of livedo is poorly understood and may be related to peripheral blood flow redistribution. Histopathological findings demonstrated endothelial activation (endothelitis) and inflammation.[7 8]

The behaviour of livedo is in many ways similar to APS. Sneddon syndrome exemplifies patients with livedo and stroke who remain persistently aPL negative. Conventionally, a diagnosis of APS is confirmed by lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and β2 glycoprotein I (β2 GPI) tests. However, routine screening of APS by LA, aCL, β2 GPI fails to identify all APS patients.[9]

Clinical features such as, pregnancy morbidity, arterial and venous thrombosis, cardiac valve abnormalities, and endothelial dysfunction are typical of patients with livedo and APS. Similarly, vasculopathy as demonstrated by abnormal ABPI may also be a common feature. Our data suggests that these features also occur in the absence of aPL and livedo reticularis may be a marker for these APS patients who remain persistently seronegative.[10]

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Table 1 Characteristics of the patients with livedo and the healthy control groups

	Livedo reticularis (n = 24)	Control group (n = 30)
Age (years)	42.5 (35–57)	39 (18–49)
Sex	All females	All females
Diabetes mellitus	1/24	1/30
Hypertension	1/24	1/30
Hyperlipidaemia	3/24	8/30
Median values:		
Serum cholesterol	5.5 (4.3–7.0 m/mol)	5.2 (3.6–6.7)
Serum low-density lipoproteins	3.2 (2.3–3.8 m/mol)	3.5 (1.9–4.7)
Serum high-density lipoproteins	1.45 (1.3–2.23 m/mol)	1.41 (0.27–2.17)
Serum triglycerides	1.4 (0.52–2.01 m/mol)	1.7 (0.57–2.11)
Smoker (or ex-smoker)	5/24	12/30
Body mass index >30	0/24	7/29
Family history of ischaemic heart disease	1/24	2/30
Pregnancy morbidity	14/24	0/30
Miscarriages	12	0
Foetal death (>10 wks)	2	0
Pre –eclampsia	3	1
Premature delivery	2	0
Still birth	1	0
Arterial thrombosis	11	0/30
Venous thrombosis	05	0/30
Abnormal ankle brachial pressure index	4/24	0/30 ($p<0.025$)

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Competing interests: None declared

Accepted 12 June 2007

Ann Rheum Dis 2008;**67**:276–277. doi:10.1136/ard.2007.074567

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Antimalarial drugs and malignancy: no evidence of a protective effect in rheumatoid arthritis

Antimalarial agents, particularly hydroxychloroquine, are frequently used drugs in rheumatology, particularly in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). A growing awareness of increased malignancies in these autoimmune rheumatic conditions has raised suspicions that drugs may alter cancer risk in such patients. In vitro, antimalarial agents have been invoked as potentially increasing[1] or decreasing[2] neoplastic processes in breast cancer cells. It has also been suggested that these drugs may decrease the in vitro activity of lymphocytic leukaemia cells.[3] However, there exists no definitive literature to show any explicit effect of antimalarial agents on cancer risk in clinical populations.

We have examined malignancy risk after antimalarial drug exposures, using a case–control design nested within a population-based cohort of 23 810 RA patients, assembled from administrative healthcare databases. Cancer cases were identified from the database records; for each case we randomly selected 10 controls, matched on age, sex and time. All exposures were assessed up to the index time (ie, cancer event in each case-control set). We used conditional logistic regression to estimate the rate ratio (RR) for the effect of antimalarial agents on malignancy risk, adjusting for disease severity and all relevant concomitant medications, including non-steroidal anti-inflammatory drugs (NSAIDs). The adjusted RR for cancer with antimalarial use was 1.1 (95% confidence interval 0.9–1.3). Thus in this very large RA sample, with appropriate methods of analyses and controlling for medication exposures, including NSAIDs, we did not see a protective effect of antimalarial agents against cancer.

A beneficial effect of antimalarial agents against malignancy in SLE has been suggested in one recent paper by Ruiz-Irastorza *et al*.[4] On the other hand, in King and Costenbade's review of lymphoma in SLE, all patients had been exposed to antimalarial agents before the development of cancer.[5] It is possible that the findings of Ruiz-Irastorza *et al* may reflect methodological issues. These authors performed a Cox proportional hazards model analysis on a cohort of SLE patients with cancer as the outcome event. They classified exposure to antimalarials as any use during the cohort follow-up (ever–never), not accounting for when this use was initiated. As has been explained previously for cohort studies,[6] such a hazards regression model will misclassify person-time in terms of exposure and cause immortal time bias. This occurs because subjects considered as "exposed" are inaccurately portrayed as contributing person-time throughout the observation interval of the study, when in fact the time before the start of exposure should be assigned to unexposed person-time. The result leads to a falsely low hazard ratio for the exposure of interest. Instead, a time-dependent Cox proportional hazards model should be used.

Another important issue is that antimalarial agents are used often in lupus pleuritis and arthritis, and are often co-administered with NSAIDs. In the study by Ruiz-Irastorza *et al*, NSAIDs were not controlled for; this is unfortunate as NSAIDs themselves protect against cancer risk and are a potential confounder of the effects of antimalarial agents.

In summary, in our very large RA sample, with appropriate methods of analyses and controlling for medication exposures, including NSAIDs, we did not find evidence of a protective effect of antimalarial drugs against cancer risk.

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Financial support: Sasha Bernatsky is the recipient of career awards from the Canadian Institutes for Health Research (CIHR), Fonds de recherche en santé du Québec FRSQ), Canadian Arthritis Net work, and of support from the McGill University Research Institute and Faculty of Medicine. Ann Clarke is an FRSQ National Scholar. Samy Suissa is the recipient of the James McGill Professorship and the CIHR distinguished investigator award.

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Accepted 1 July 2007

Ann Rheum Dis 2008;**67**:277–278. doi:10.1136/ard.2007.075705

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Ann Rheum Dis 2008 67: 276-277
doi: 10.1136/ard.2007.074567